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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/053,474	11/02/2001	Gerardo Castillo	PROTEO.P17	3722

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EXAMINER	
TURNER, SHARON I.	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 04/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/053,474	CASTILLO ET AL.	
	Examiner	Art Unit	
	Sharon L. Turner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *9 and 11-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-21* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restriction

1. Applicant's election of Group I, claims 1-8 and 10, in the Paper of 1-22-04 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). The Examiner notes that Applicant's referral to the election as an election of species is in error. The restriction requirement was set forth in patentably distinct groups, and not as an election of species.

2. Claims 9 and 11-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected, there being no allowable generic or linking claim. Election was made **without** traverse in the Paper of 1-22-04.

Specification

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The elected claims are directed to a method of detection or diagnosis and not to treatment.

4. The brief description of the drawings should be amended to reflect the views, i.e., Figures 1A-B, 2A-C, 3A-B, 4A-D, 5A-D and 6A-D.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-8 and 10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification describes at p. 3, lines 4-19 a particular antibody derived from a clone library designated HS4C3 which is referred to as PTI-HS7. The specification discloses proteins to which the antibody exhibits no reactivity as well as proteins to which the antibody binds. The specification discloses that the initial studies suggest that sulfate and particularly O- and N-sulfate in heparan sulfate/heparan/heparin glycosaminoglycans are important for recognition.

The claims are directed to "PTI-HS7 antibody" and to "PTI-HS7 antigen". However, the specification fails to particularly define that which is the "PTI-HS7 antibody" and fail to disclose that which is the "PTI-HS7 antigen". Antibodies and antigens are generally described by their epitope structure and specificity. Yet in instant case no such structure or function is delineated within the claims. Thus, the artisan has no guidance as to that which corresponds to a PTI-HS7 antibody or antigen and would be unable absent such guidance to distinguish it amongst any other antibody antigen combination. While the specification provides some guidance as to the HS4C3 clone, such is not the subject of the claims and the limitations provided within the specification cannot be read into the claims. Thus, the recitations lack adequate written description support.

A genus claim may be supported by a representative number of species as set

forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention". Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id at 1170, 25 USPQ2d at 1606."

The instant specification discloses a single isolated antibody but fails to

distinguish it except by name. No particular structure, function or binding specificity of the antibody is noted other than its purported use in detection or diagnosis of amyloid disease.

7. Claims 1-8 and 10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification lacks complete deposit information for the deposit of antibody PTI-HS7 derived from the clone designated as HS4C3, see in particular p. 3, lines 4-10. Because it is not clear that antibodies possessing the properties of PTI-HS7 or clone HS4C3 are known and publicly available or can be reproducibly isolated from nature without undue experimentation, and because the claims require the use of PTI-HS7 derived from clone HS4C3, a suitable deposit for patent purposes is required. Accordingly, filing of evidence of the reproducible production of the antibody claimed in claims 1-8 and 10 is required. Without publicly available deposit of the antibody producing clone, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication is an unpredictable event.

Applicant's referral to the clone at page 3 of the specification is an insufficient assurance that all required deposits have been made and all the conditions of 37 CFR § 1.801-1.809 have been met.

If the deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of the patent on this application. These requirements are necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State. Amendment of the specification to recite the date of deposit and the complete name and full street address of the depository is required.

If the deposits have not been made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR § 1.801-1.809, assurances regarding availability and permanency of deposits are required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the

authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request;

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application;

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non replicable.

In addition, a deposit of biological material that is capable of self-replication either directly or indirectly must be viable at the time of deposit and during the term of deposit. Viability may be tested by the depository. The test must conclude only that the deposited material is capable of reproduction. A viability statement for each deposit of a biological material not made under the Budapest Treaty must be filed in the application and must contain:

1) The name and address of the depository;
2) The name and address of the depositor;
3) The date of deposit;
4) The identity of the deposit and the accession number given by the depository;
5) The date of the viability test;
6) The procedures used to obtain a sample if the test is not done by the depository; and
7) A statement that the deposit is capable of reproduction.

As a means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the deposit was made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the HS4C3 clone that produces antibody PTI-HS7 described in the specification as filed is the same as that deposited in the depository. Corroboration may take the form of a showing of a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundack, 773F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR § 1.801-1.809 for further information concerning deposit practice.

8. Claims 6-7 and 10 are rejected under 35 U.S.C. 112, first paragraph, because

the specification, while being enabling for detection of amyloid associated diseases via detection of heparan sulfate glycosaminoglycan using antibody PTI-HS7 in amyloid disease affected tissue, does not reasonably provide enablement for diagnosis of such diseases in biological fluid, blood, plasma, serum, cerebrospinal fluid sputum, saliva, urine and stool or without such pathological comparison as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specifications disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation. The factors relevant to this discussion include the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims.

The specification notes particular staining using haparan sulfate glycosaminoglycan antibody in amyloid associated diseases as recognized in the art of record, see in particular Su et al., Neuroscience (1992 Dec) 51(4):801-13, Buee et al., Acta neuropathologica (1994) 87(5) :469-80, and Ginsberg et al., J. of Neuropath. & Exp. Neurol., (1999 Aug) 58(8):815-24. Such teachings exemplify that it is the association of heparan sulfate glycosaminoglycan immunoreactivity within pathogenic accumulations associated with mucopolysaccharidosis and amyloid deposition diseased patients, in comparison to controls, that allows for the identification of, prognosis or diagnosis of diseased states. The art further recognizes that heparan sulfate

glycosaminoglycan immunoreactivity is not only associated in such disease states but is also normally expressed in extracellular components of various tissues including basement membranes of kidney, muscle, glomerulus, connective tissue and in synaptic membranes, see in particular Van Kuppevelt et al., J. of Biol. Chem., (May 22, 1998) 273(21):12960-66, Bayne et al., J. of Cell Biol., (1984 Oct) 99(4 Pt 1):1486-501, Miettinen et al., J. of Exp. Med., (1986 May 1) 163(5):1064-84, Klein et al., J of Cell Biol., (1988 March) 106(3):963-70, Elam et al., Neurochem. Res., (1988 Aug) 13(8):715-20 and Heremans et al., J of Cell Biol., (1989 Dec) 109 (6 Pt 1):3199-211. Thus, mere detection of such binding as in claim 10 fails to necessarily denote amyloid disease. In contrast such detection is normal in particular tissues as exemplified above.

The Examiner's search of the prior art fails to recognize heparan sulfate glycosaminoglycan in biological fluids in either normal or amyloid diseased patients. The specification further fails to exemplify such expression. While Applicants methodology may be capable of detecting heparan sulfate in such fluids, the artisan is not apprised that such expression would be considered correlative in amyloid diseased patients. In contrast such expression may be relevant to normal excretion. Yet neither the prior art nor the specification provide guidance whereby the artisan could conclude that such expression was either normal or indicative of the diseased state. Thus, absent further guidance the artisan is not assured of the ability to make and use the invention within the full scope of the claims.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the

changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986). Thus, the skilled artisan cannot readily make and use the claimed methods without further undue experimentation.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior

art under 35 U.S.C. 103(a).

10. Claims 1-5, 8 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van Kuppevelt et al., J. of Biol. Chem., (May 22, 1998) 273(21):12960-66, Su et al., Neuroscience (1992 Dec) 51(4):801-13, Buee et al., Acta neuropathologica (1994) 87(5) :469-80, Ginsberg et al., J. of Neuropath. & Exp. Neurol., (1999 Aug) 58(8):815-24, and Benjamini and Leskowitz, Immunology: A short course, 2nd Ed., Wiley-Liss, NY, NY, pp. 117-121, 1991.

Su et al., Neuroscience (1992 Dec) 51(4):801-13 teach immunohistochemistry of brain tissue samples with heparan sulfate glycosaminoglycan antibody to detect such deposition in Alzheimer's diseased brain associated with and co-localized with beta-amyloid protein. Su et al., notes that the level (number and intensity) of such deposits were greater in Alzheimer's samples in comparison to control sections from normal brain and suggest such analysis as a marker for the pathological changes associated in Alzheimer's patients, see in particular Abstract, Figures 1-5, Results and Discussion.

Buee et al., Acta neuropathologica (1994) 87(5) :469-80 teach immunohistochemistry of brain tissue samples with heparan sulfate reactive antibody to detect such deposition in amyloid associated diseases and depositions associated in Alzheimer's, Down syndrome, Guam amyotrophic lateral sclerosis, Parkinsonian dementia complex, Pick's disease and dementia pugilistica. In all diseased tissues increased levels of staining were associated with increased microvascular pathology in comparison to normal controls, see in particular Figures 1-6 and Discussion. Buee notes particular staining staining in diseased states in comparison to normal controls

and thus evidence staining indicative of the amyloid associated diseases.

Ginsberg et al., J. of Neuropath. & Exp. Neurol., (1999 Aug) 58(8):815-24 teach immunohistochemistry of brain tissue samples with heparan sulfate reactive antibody to detect deposition in amyloid associated diseases such as Alzheimer's disease, Down Syndrome, Hurler's syndrome (Mucopolysaccharidosis (MPS) I), Sanfillippos's syndrome (MPS III), caprine MPSIIID and murine MPS VII models. Analysis shows that many of the diseased tissues show the prevalence of beta-amyloid associated plaques within those portions exhibiting the increased staining of heparan sulfate antibodies, see in particular Tables I-II, Figures 1-5 and Discussion. Ginsberg et al., note the prevalence of heparan sulfate proteoglycan staining in associated with the diseased pathology of mucopolysaccharidosis as well as in Alzheimer's and Down's syndrome patients as well as being associated with and indicative of such pathological changes associated with disease, see in particilar, Discussion pp821-22.

Neither Su, Buee or Ginsberg note detection with radiolabeled antibody or with the specific heparan sulfate glycosaminoglycan reactive antibody PTI-HS7.

Van Kuppevelt et al., teach antibody produced via clone HS4C3 reactive with heparan and heparan sulfate glycosaminoglycans, see in particular abstract, Figures 1-2 and Tables I-II. The HS4C3 antibody is equivalent to PTI-HS7 as supported by the specification at p. 3, lines 4-19 and provides the advantage that it is easily reproduced in clonal form.

Benjamini and Leskowitz, Immunology: A short course, 2nd Ed., Wiley-Liss, NY, NY, pp. 117-121, 1991 teach immunodetection via radioimmunoassays wherein the

antibodies within a particular antigen-antibody interaction are detected via the use of an isotopic radiolabel. The procedure is noted to be advantageous in that it allows measurements of extremely small amounts of antibody or antibody antigen complex. Detection is via radioactivity and thus the detection sensitivity is increased several orders of magnitude and is easily detected and quantitated in the laboratory.

Thus, given the cumulative reference teachings one of skill in the art would be motivated to substitute the HS4C3/PTI-HS7 clonal antibody for the heparan sulfate antibodies utilized in the Su, Buee or Ginsberg references because the clonal antibody is easily produced in high quantity and purity and provides the advantages of a clonal antibody that eliminates variability amongst different antibody preparations. Clonal antibodies are particularly useful for standardized testing as noted by Van Kuppevelt. One of skill in the art would further be motivated to use detection of the HS4C3/PTI-HS7 antibody using a radiolabel because of the increased sensitivity in detection using the isotopic label. Radioisotopes may be easily quantified in the laboratory and allow comparison of levels in a standardized assay. One of skill in the art would have expected positive results using the methods of Su, Buee and Ginsberg with the improvements of detection with HS4C3/PTI-HS7 given the exemplifications of Ban Kuppevelt teaching the specificity of the antibody for heparan sulfate glycosaminoglycan and the teaching of Benjamini and Leskowitz that improved detection may be achieved using the enhanced sensitivity of radiolabel for detection of antigen/antibody complexes. Thus, the cumulative reference teachings render the claimed invention obvious to the artisan.

Status of Claims

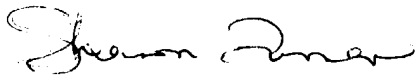
11. No claims are allowed.

12. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (571) 272-0894. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached at (571) 272-0887.



Sharon L. Turner, Ph.D.
April 13, 2004